学位論文の要旨

Effect of Impaired Renal Function on the Maintenance Dose of Warfarin in Japanese

（日本人において腎機能低下がワルファリン維持量に及ぼす影響）

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Introduction

Impaired renal function alters the dose-effect relationship not only for drugs that are excreted by the kidney, but also for some drugs that are metabolized primarily by the liver and not renally excreted (Dreisbach and Lertora, 2008, Nolin et al., 2008). Warfarin is one such drug that is eliminated through hepatic metabolism and not directly excreted by the kidney (Ufer et al., 2004). Recent studies reported that patients with impaired renal function had lower maintenance doses of warfarin than those with normal renal function in cohorts which consisted primarily of African and European Americans (Limdi, N. A. et al., 2009, Limdi, Nita A. et al., 2010). In Asian patients, however, the effect that decreased kidney function has on the maintenance dose of warfarin remains unclear. It is also unknown whether the maintenance dose of warfarin can be predicted more accurately by including renal function along with conventional demographic and genetic variables in Asians.

In this cross-sectional study in Japanese patients, we examined: [1] whether the maintenance dose of warfarin has a correlation with renal function that is independent from other demographic, clinical, and genetic variables; and [2] whether the maintenance dose of warfarin can be predicted more accurately by including renal function along with other variables.

Materials and Methods

Japanese patients who were receiving a constant dose of warfarin for 3 months or longer and had a prothrombin time/international normalized ratio (PT-INR) of 1.5 to 3.0 on at least three consecutive visits during the same period were included. Patients who had either liver dysfunction, serum aminotransferase levels at least twice the upper limit of normal, or who were receiving chronic renal replacement therapy (e.g., hemodialysis) were excluded.

Estimated creatinine clearance (eCrCl) was used as an estimate of kidney function of the patients based on clinical information. In addition, we categorized the patients into three groups based on their estimated glomerular filtration rate (eGFR). Estimated GFR ≥60 ml/min/1.73 m^2 were categorized as categories G1/G2; eGFR of ≥30 to <60 ml/min/1.73 m^2 as categories G3a/G3b; and eGFR <30 ml/min/1.73 m^2 as categories G4/G5.

Results

There were 137 patients who fulfilled the conditions of the protocol and gave informed consent to participate in the study. The average dose of warfarin was 3.21 ± 1.46 mg/day. The average of eCrCl was 62.5 ± 25.5 ml/min.

Warfarin dose was positively correlated with eCrCl ($p < 0.0001$, $r^2 = 0.23$).

There was a significant difference between the warfarin doses in patients with different categories of eGFR ($p < 0.01$). In a post-hoc comparison, warfarin doses in patients in eGFR categories G3a/G3b and G4/G5 were found to be significantly lower than that in patients in eGFR categories G1/G2 (2.88 ± 1.42 and 2.33 ± 1.04 mg/day vs. 3.54 ± 1.44 mg/day, $p < 0.05$). Patients in eGFR categories G4/G5 ($n = 9$) had a slightly, but not significantly lower warfarin dose than those in eGFR categories G3a/G3b ($p = 0.28$).

Based on a stepwise linear regression, age, body weight, genotype of *VKORC1* -1639 G>A polymorphism, eCrCl, and intra-individual average PT-INR were chosen as independent variables for a formula to predict warfarin maintenance dose. The derived formula with estimated parameters was as follows:

Predicted warfarin maintenance dose (mg/day) =

(-0.652)
+ (-0.026) × age (years)
+ (0.044) × body weight (kg)
+ (1.861) (if *VKORC1* -1639 G>A genotype is not AA)
+ (0.016) × eCrCl (ml/min)
+ (0.747) × target PT-INR

The coefficient of determination (r^2) of this formula was 0.47. A regression equation with all the same explanatory variables except for eCrCl had an r^2 of 0.41.

Discussion

We demonstrated for the first time to our knowledge, that eCrCl was positively correlated with warfarin maintenance dose in Asian patients. Warfarin doses in patients in eGFR categories G3a/G3b and G4/G5 were found to be significantly lower than that in patients in eGFR categories G1/G2. In a multivariate regression, adding eCrCl to age, body weight, *VKORC1* -1639 G>A genotype, and intra-individual average PT-INR as an independent variable increased accuracy in predicting warfarin dose.

References

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論文目録

Ⅰ 主論文

Effect of Impaired Renal Function on the Maintenance Dose of Warfarin in Japanese
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Ⅱ 副論文

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Ⅲ 参考論文

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